UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/378,577	08/20/99	SHI	W 60307-5001

HM12/0126
JEFFER MANGELS BUTLER & MARMARO LLP
TENTH FLOOR
2121 AVENUE OF THE STARS
LOS ANGELES CA 90067

EXAMINER	
ZEMAN, R	
ART UNIT	**PAPER NUMBER**
1645	

DATE MAILED: 01/26/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
09/378,577	Shi et al.
Examiner	**Group Art Unit**
Robert A. Zeman	1645

☒ Responsive to communication(s) filed on *Oct 12, 2000* .

☒ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *1-17* is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-17* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____ .

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____ .

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☐ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

Applicant's amendment filed on October 12, 2000 is acknowledged. It should be noted that said amendment was only partially entered since the proposed changes to claims 1 and 7 fail to comply with Rule 1.121. Said rule states that proposed amendments to claims of greater than 5 words require said claims to be rewritten.

Claim Objections

The objection to claims 13-16 for having the word "eukaryote" is misspelled is withdrawn in light of the amendment thereto.

Claim Rejections Withdrawn

35 USC § 112

The rejection of claims 3-5, 9-11 and 13-16 under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the production of IgG monoclonal antibodies by transformed plants, does not reasonably provide enablement for the production of IgM monoclonal antibodies by said plants is withdrawn in light of Applicants arguments which have been found to be persuasive.

Claim Rejections Maintained

35 USC § 112

The rejection of claims 5, 11 and 13-16 under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the topical treatment using chimeric monoclonal antibodies, does not reasonably provide enablement for the treatment for the oral ingestion of tissue from transformed host is maintained for reasons of record.

Applicant argues that the state of the art in genetic manipulation of expression in plants is far more developed than is suggested by Examiner's comments. Specifically, Applicant cite two references (Thomzik, *Agrobacterium*-mediated Transformation of Stem Disks from Oilseed Rape (*Brassica napus* L.) and Topping et al., *Agrobacterium*-mediated Transformation of *Arabidopsis thaliana*) to "demonstrate the similarity of the techniques used to transform the respective plants and thereby express foreign proteins. Applicant further argues that the teachings of Thomzik demonstrates that the transformation of *Brassica* was known in the art at the time of the instant invention. Applicant further argues that "the absence of a specific disclosure of a method for expressing monoclonal antibodies in *Brassica* should not be viewed as a lack of enablement because those skilled in the art would be able to transform *Brassica* using the teachings of the specification. Applicant cites articles by Tacket et al. (Nature Medicine, Vol. 4, pages 607-609) and Kipriyanov et al. (Molecular Biology, Vol. 12, pages 173-201) to illustrate the state of the art. Tacket et al. is cited since they disclose the expression of viral antigens by transgenic potatoes, while Kipriyanov et al. is cited since the proclaim "plants are capable of synthesizing

and assembling virtually every kind of antibody molecule, ranging from the smallest antigen-binding domains and fragments to full length and even multimeric antibodies". Applicant concludes by stating that the aforementioned references indicate the state of the art is broader than asserted by Examiner and hence the rejection should be withdrawn.

Applicant's arguments have been fully considered and have been found to be non-persuasive. While Applicant is correct that in stating that Thomzik discloses the transformation of Oilseed Rape (*Brassica napus* L.) using *Agrobacterium*, the basis for his assertion that said methods are the same as those for transforming *Arabidopsis* is not understood. In fact, Thomzik teaches the opposite. On page 79, first paragraph, Thomzik states "Transformation protocols are relatively specific for cv. Westar and cannot be extended to most of the other spring and none of the winter varieties.....". Since the disclosed protocols only are effective with certain varieties within the same species, it is extremely remote that said protocols would be effective in another species. With regard to the teachings of Tacket et al. and Kipriyanov et al., Tacket discloses the expression of viral antigens (not antibodies) in a species of plant unrelated to *Brassica*. Additionally, Kiprayanov's assertion cannot be construed to mean that "all plants can express all antibodies". Consequently, the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. Applicant describes procedures for the use of *Arabidopsis thaliana* for the production of human/mouse chimeric monoclonal antibodies with

specificity for *Streptococcus mutans*. Applicant fails to describe what procedures would be used when the plant species *Brassica*, or other edible plant, is used in lieu of *Arabidopsis*.

The rejection of claims 3 and 9 under 35 U.S.C. 112, second paragraph, as being vague and indefinite through the use of the phrase "step of preparing" is maintained for reasons of record. Applicant argues that it is obvious that the "preparing step" refers to the chimeric antibodies of the antecedent claim. Applicant's arguments have been fully considered and have been found to be non-persuasive. As stated in the original rejection, it is unclear precisely what the "step of preparing" is referring to. It is suggested that "wherein the step of preparing further comprises..." be changed to "wherein step c) further comprises".

35 USC § 102

The rejection of claims 1, 6 and 7 under 35 U.S.C. 102(b) as being anticipated by Lehner (U.S. Patent 5,352,446) is maintained for reasons of record. Lehner discloses the use of a orally administered murine monoclonal antibody (see column 3 lines 46-52 and column 4, lines 4-13) for the treatment and prevention of dental caries in man (see column 2, line 31-32). Lehner further discloses that said monoclonal antibody has a specificity for *Streptococcus mutans* and can be administered in gum, mouthwashes, or lozenges. Additionally, Lehner discloses that monoclonal antibodies against *S. mutans* antigens passively immunize and provide inhibition of the development of *S. mutans* on teeth for extended periods of time when applied topically (see column 2, lines 16-21).

In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., monoclonal antibodies are chimeric) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

35 USC § 103

The rejection of claims 1-4, 6-10, 12 and 17 under 35 U.S.C. 103(a) as being unpatentable over Ma et al. (European Journal of Immunology 1994 Vol. 24 (1) pages 131-138) in view of Adair et al (U.S. Patent 5,877,293) is maintained for reasons of record. As previously stated in the previous office action Ma et al. disclose methods for the production of chimeric monoclonal antibodies against *Staphylococcus mutans* in transgenic tobacco plants to be used in the treatment of dental caries in humans and other mammals (see page 131, second paragraph). The disclosed methods include: the cloning of heavy and light chain genes (see page 132); plant transformation and regeneration (see page 132); antibody chain detection (see pages 132-133); and measurement of chimeric antibodies and their binding capacities (see pages 133-134). Ma et al. differs from the claimed inventions in that both the heavy and light chains of the chimeric monoclonal antibodies are derived from murine antibodies. However, Adair et al. disclose methods for the production of chimeric antibodies where the light chains are derived from murine antibodies and the heavy chains are derived from human antibodies. Consequently, it would have

been obvious to one of skill in the art at the time the invention was made to use the methods of Adair et al. to "humanize" the chimeric antibodies disclosed in the methods of Ma et al. This "humanizing" consists of replacing the murine heavy chain sequences of Ma et al. with the human heavy chain sequences of Adair et al. in the expression vectors of Ma et al. It should be noted that humanizing antibodies is a standard procedure used in most immunology laboratories. That, and coupled with the fact that Ma et al. suggests "incorporating other regions such as the complement binding region of human IgG" (see page 137, second paragraph) and Adair et al. state that chimeric monoclonal antibodies are less antigenic to humans and hence more effective therapeutically (see column 1 lines 52-65), one would have a high expectation of success in making the required antibodies and using them to treat or prevent dental caries.

Applicant argues that the antibodies disclosed by Ma et al. differ from those of the instant invention in that the antibodies of Ma et al. are entirely murine in origin. Applicant further argues the humanization of the antibodies, as disclosed by Adair et al, merely reduces the incidence of HAMA and does not engage the effector apparatus of the human immune response. Applicant further states that the combination of the cited references would not teach or suggest the instant invention. Applicant concludes by arguing the cited references do not teach or suggest the use of chimeric antibodies to bring the effector apparatus of the human immune system to bear on an infectious or otherwise pathological site in the body. Applicant's arguments have been fully considered and have been found to be non-persuasive. Applicant is reminded that the aforementioned rejection is based on the combination of the cited references (see above) and not

independently. Said combination clearly encompasses all the limitations of the claimed invention. Additionally, as pointed out by Applicant, the construction of chimeric and humanized antibodies and the tailoring of the constant regions (i.e. selection of isotypes specific for cell mediated cytotoxicity) is well known in the art (see Kipriyanov et al.,Molecular Biology, Vol. 12, pages 173-201).

Conclusion

No claim is allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Robert A. Zeman whose telephone number is (703) 308-7991. The examiner can be reached between the hours of 7:30 am and 4:00 pm Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, Donna Wortman, Primary Examiner can be reached at (703) 308-1032 or the examiner's supervisor, Lynette Smith, can be reached at (703)308-3909.

DONNA WORTMAN
PRIMARY EXAMINER

Robert A. Zeman

January 25, 2001